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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/082,112	05/20/1998	ALBERTO L. MENDOZA	MSU4.1-406	2322

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EXAMINER	
GANGLE, BRIAN J	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/082,112	MENDOZA, ALBERTO L.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 9/26/2005 has been entered.

Claims 16-25 are pending and under examination.

It is noted that the examiner of record has changed. Please address all future correspondence to Examiner Brian Gangle, Art Unit 1645.

All previous grounds of objection or rejection are withdrawn in favor of the new grounds of rejection set forth herein.

Applicant's remarks filed 7/13/2005 appear to be a copy of remarks filed 12/27/2001 which were previously considered in the action dated 2/11/2002. Further, the issues raised have been addressed by the Board of Appeals. See decision issued on 1/5/2005.

Specification

The amendment filed 10/8/1999 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment changes the strain of *Pythium insidiosum* from ATCC strain 58643 to ATCC strain 74446. This is deemed new matter lacking specific written description support in the specification as filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As to claim 16 and dependent claim 17, claim 16 has been amended to include the precipitation of proteins with acetone. The claim is drawn such that the vaccine contains "intracellular proteins consisting essentially of proteins removed from disrupted cells of the *Pythium insidiosum* grown in a culture medium," and also of "extracellular proteins which consist essentially of proteins removed from the culture medium for growing the *Pythium insidiosum* by having been precipitated together from the culture medium with acetone." The specification describes a method of vaccine production (pp. 6-8) wherein supernatant from disrupted cells is mixed with the culture medium of said cells. Acetone is then used to precipitate proteins from that mixture. Thus, the use of acetone to precipitate proteins from Pythium culture medium before mixing with intracellular proteins removed from disrupted cells is deemed new matter lacking specific written description support in the specification as filed.

As to claim 18, and dependent claims 20-22, claim 18 has been amended include the use of acetone to precipitate proteins from culture medium. The claim includes a vaccine "wherein the admixture of proteins has been precipitated from the culture medium with acetone." The components of the vaccine are: 1. mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* separated from the culture medium; and 2. mixed extracellular proteins, which consist essentially of proteins removed from the culture medium separated from the cells of the *Pythium insidiosum*." Acetone is used here to precipitate proteins from the culture medium. Since component 1 contains proteins from cells that have been removed from culture medium, acetone could only be used to precipitate proteins from component 2. The specification describes a method of vaccine production (pp. 6-8) wherein supernatant from disrupted cells is mixed with the culture medium of said cells. Acetone is then used to precipitate proteins from that mixture. Thus, the use of acetone to precipitate proteins from Pythium culture medium before mixing with intracellular proteins removed from disrupted cells is deemed new matter lacking specific written description support in the specification as filed.

As to claim 21, the claim as originally filed recites *Pythium insidiosum* ATCC strain 58643, whereas the amendment filed 10/8/1999 changes the strain to ATCC strain 74446. This is deemed new matter lacking specific written description support in the specification as filed.

Claim18, and dependent claims 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is drawn to a method for the treatment of Pythiosis using a vaccine which comprises an admixture of 1. mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* separated from the culture medium; and 2. mixed extracellular proteins, which consist essentially of proteins removed from the culture medium separated from the cells of the *Pythium insidiosum*; wherein the admixture of proteins has been precipitated from the culture medium with acetone and admixed with water. The method steps of the claim are unclear. Component 1 consists of proteins that have been removed from cells that have been removed from the culture medium. Component 2 consists of proteins

that have been removed from culture medium. The claim requires that the "admixture of proteins be precipitated from the culture medium" using acetone. Component 1 does not contain culture medium, thus the acetone precipitation must occur in component 2. However, it appears from step (a) that the "admixture" is a mixture of intracellular and extracellular proteins. Thus it is unclear what the "admixture" consists of and when the acetone precipitation actually occurs.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18, 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendoza *et al.* (92a)(Mycopathologia 119:89-95, 1992) in view of Mendoza *et al.* (92b)(J. Clinical Microbiol, 30:2980-2983, 1992), Mendoza (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog.

The instant claims are drawn to a method for the treatment of Pythiosis in a mammal which comprises injecting a vaccine comprising:

1. mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of *Pythium insidiosum* separated from the culture medium; and
2. mixed extracellular proteins, which consist essentially of proteins removed from the culture medium separated from the cells of the *Pythium insidiosum*;

wherein the admixture of proteins has been precipitated from the culture medium with acetone and admixed with water and then has been dialyzed to remove low molecular weight components less than 10,000 MW (claim 18). Further limitations include the method of claim 18 where the cells have been disrupted by sonication (claim 20), where the *Pythium insidiosum* is deposited as ATCC 74446 (claim 21), and where the culture medium is Sabouraud's dextrose broth (claim 22).

At the outset, the examiner notes the 35 U.S.C. 112, second paragraph rejection with respect to the current amendments. For this rejection, the cells of claim 18 are removed from the culture medium before the intracellular proteins are separated from the disrupted cells. The acetone precipitation is performed to remove proteins from the culture medium and is thus used to remove the extracellular proteins from the culture medium.

Mendoza *et al.* (92a) teach subcutaneous vaccination of mammals with two vaccines for pythiosis, the Cell Mass Vaccine (CMV), and the Soluble Concentrated Antigen Vaccine (SCAV). The CMV consists of mixed intracellular antigens of *P. insidiosum* obtained by culturing *P. insidiosum* (ATCC 58643) in Sabouraud's dextrose broth. The cells were removed from the culture medium and disrupted by homogenization to provide the antigens for the vaccine (p. 90, col. 2). The SCAV consists of extracellular proteins obtained by culturing *P. insidiosum* (ATCC 58643) in Sabouraud's dextrose broth. The extracellular antigens were concentrated with a stir cell and precipitated with acetone (p. 91, col. 2 and p.92 col. 1). Mendoza *et al.* (92a) teach that both vaccines were successful in curing cases of pythiosis in horses (p. 91, col. 2, paragraph 2). Mendoza *et al.* (92a) further teaches that the etiological agent of pythiosis in horses, cattle, dogs, cats, and humans is *Pythium isidiosum*, and that nine strains isolated from humans, horses, and dogs with the disease were all the same species (p. 89, paragraph 1). Mendoza *et al.* (92a) does not teach that the intracellular proteins are separated from the disrupted cells in the CMV or the use of sonication to disrupt the cells. Mendoza *et al.* (92a) further does not teach the use of dialysis to remove components less than 10,000 MW or a vaccine that is a mixture of the intracellular and extracellular proteins.

Mendoza *et al.* (92b) teach alternative methods to produce intracellular and extracellular protein pythiosis vaccines. The vaccine containing the intracellular proteins was produced by culturing *P. insidiosum*, killing the cells with Methiolate (thimersol), sonicating the cells to disrupt them and release intracellular proteins, then separated from the cell debris by centrifugation (p. 2981, col. 1, paragraph 1). An alternative method to produce a vaccine containing extracellular proteins is also taught. Cultures were killed with Merthiolate (thimersol), filtered to remove cells, and a stir cell with PM-10 membrane (Amicon) was used to concentrate the antigen (and remove low molecular weight components)(p. 2981, col. 1, paragraph 2). They also teach the important antigens found in the CMV vaccine and disclose

that in addition to three immunodominant proteins (32K, 30K, and 28K) there are at least 20 antigens found in the intracellular proteins of *Pythium isidiosum* that are reactive in horse sera (p. 2981, col. 2, paragraph 3) and suggest that vaccines should include the three immunodominant proteins (p. 2982, col. 2, paragraph 3). Mendoza *et al.* (92b) also teach that five strains of *Pythium isidiosum* all had similar intracellular protein profiles.

Mendoza (95) teaches a vaccine that combined extracellular pythium antigens and the three immunodominant intracellular proteins of Mendoza (92b) and that said vaccine had an enhanced therapeutic effect on horses (see abstract). Mendoza (95) further teaches that hyphal antigens may contain products that are directly involved in the enhancement of the immunological response to vaccination (see abstract).

The Amicon 1993 catalog teaches that a PM10 membrane will retain molecules larger than 10,000 MW (p. 35).

The Fisher 1995 catalog teaches dialysis membranes which will retain molecules larger than 10,000 MW (p. 56).

As to claims 18, 20-22, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to vaccinate mammals with a pythiosis vaccine comprising a mixture of mixed intracellular proteins (especially including the three immunodominant proteins of Mendoza (92b)) and mixed extracellular proteins because Mendoza (95) teaches that a vaccine comprising a mixture of three immunodominant intracellular proteins and extracellular proteins was more successful in curing horses than either the CMV or SCAV vaccines, and because Mendoza (92b) teaches that there are at least 20 reactive antigens found in the intracellular proteins of *Pythium isidiosum* that might be useful in immunotherapy. It would also have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to use the method obtain the intracellular antigens by culturing *P. insidiosum*, killing the cells with Methiolate (thimersol), sonicating the cells to disrupt them and release intracellular proteins, then separated from the cell debris by centrifugation because it would be easier to obtain the intracellular proteins this way, than using electrophoresis to obtain only the three immunodominant proteins. The ordinary artisan would also have been motivated to use dialysis instead of a stir-cell with a PM10 membrane because dialysis is significantly cheaper and provides for large batches. Further, as taught by the Amicon and Fisher catalogs, the removal of

small molecules of less than 10,000 MW by the PM10 membrand and the dialysis membrane is functionally equivalent.

Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendoza *et al.* (92a)(Mycopathologia 119:89-95, 1992), Mendoza *et al.* (92b)(J. Clinical Microbiol, 30:2980-2983, 1992), Mendoza (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog as applied to claims 18, 20-22 above, and further in view of Mendoza *et al.* (J. Mycol. Med., 6:151-164, 1996).

Mendoza *et al.* (92a), Mendoza *et al.* (92b), Mendoza (95), Amicon 1993 catalog, and Fisher 1995 catalog as combined over claims 18, 20-22 is set forth *supra*. The combination as set forth *supra* does not teach the treatment of pythiosis in humans using the vaccine as set forth above.

Mendoza *et al.* (96) teach the prevalence of human pythiosis and the need for an effective treatment for humans (p. 156, col. 2 and p. 160, col. 2, paragraph 2). They also teach the benefits of vaccination using intracellular (CMV) and extracellular (SCAV) antigens from *P. insidiosum* (p. 161, Immunotherapy). Mendoza *et al.* (96) further teach similarities in *P. insidiosum* antigens detected in human and horse sera (p. 159, Immunodiffusion test).

As to claims 16-17, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to use the mixed intra and extracellular vaccine combination set forth *supra* to treat humans because of the similarity in antigenicity and serological reactivity in humans to that found in horses, because of the increased benefit seen by the combination in horses, and by the need for an effective treatment in humans.

Claims 19, 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendoza *et al.* (92a)(Mycopathologia 119:89-95, 1992), Mendoza *et al.* (92b)(J. Clinical Microbiol, 30:2980-2983, 1992), Mendoza (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog as applied to claims 18, 20-22 above, and further in view of Blanch *et al.* (Biochemical Engineering, Marcel Dekker, Inc., 1996).

Mendoza *et al.* (92a), Mendoza *et al.* (92b), Mendoza (95), Amicon 1993 catalog, and Fisher 1995 catalog as combined over claims 18, 20-22 is set forth *supra*. The combination as set forth *supra* does not teach the use of acetone to precipitate proteins after the intracellular proteins have been mixed with the extracellular proteins.

Blanch *et al.* teach that one of the most common methods of precipitating proteins is through the addition of acetone, and that it is usually preferred over longer-chain organics (p. 491, paragraph 4 and p. 496, paragraph 2).

As to claims 19, 22-25, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to use acetone to precipitate the proteins of the invention because it is standard in the art to use acetone precipitation and because Blanch *et al.* teach that one of the most common methods of precipitating proteins is through the addition of acetone.

Status of the Claims

All claims stand rejected.

Citation of Relevant Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. ATCC product description for strain ATCC 74446 and ATCC 58643 (http://www.atcc.org). The catalog teaches that Strain ATCC 74446 is a redeposit of strain ATCC 58643.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Gangle whose telephone number is 571-272-1181. The

examiner can normally be reached on M-F 8:00 am - 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

BG

Brian Gangle
AU 1645

PATRICIA A. BUFFY
PRIMARY EXAMINER